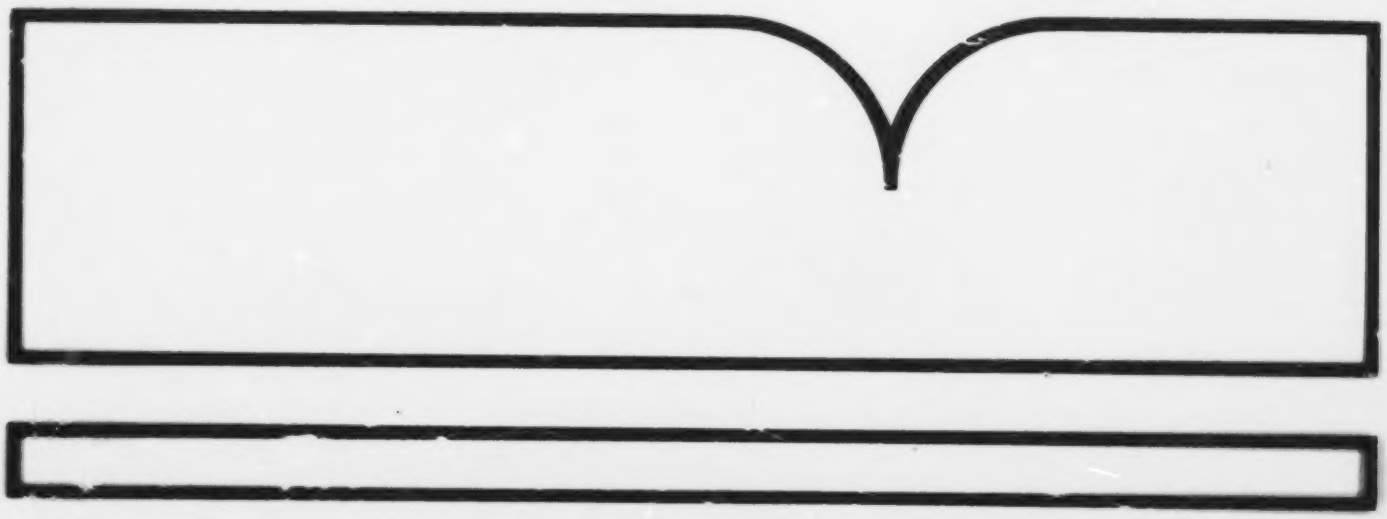
PB90-259920

Triallate: Decision Document

(U.S.) Environmental Protection Agency, Washington, DC

Nov 80



U.S. Department of Commerce
National Technical Information Service
NTIS

540/09-90-101

PB90-259920

TRIALLATE

DECISION DOCUMENT

NOVEMBER 1980

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

ENVIRONMENTAL PROTECTION AGENCY
401 M STREET S.W.
WASHINGTON, DC 20460

Acknowledgments

PROJECT TEAM

Gary Baker, Project Manager, SPRD
Karl Bayer, Attorney, OGC
W. Thomas Edwards, Toxicologist, HED
Karen Flagstad, Writer-Editor, SPRD
Janice Jensen, Chemist, HED
Charles Lewis, Agronomist, BFSD
Irving Mauer, Toxicologist, HED
Abraham Mittelman, Chemist, HED

Esther Saito, Acting Section Head, SPRD
David Severn, Chemist, HED
Minnie Sochard, Project Manager, SPRD
Linda V. Zyadlo, Economist, BFSD

EPA PESTICIDE CHEMICAL REVIEW COMMITTEE (PCRC)

Charles Gregg, OWWPM
Richard N. Hill, OPTS
Allen L. Jennings, OPM
Donna R. Kuroda, ORD
John J. Neylan, OE
Edward Tuark, OANR
Marcia Williams, Chairperson, SPRD, OPTS
Michael Winer, OGC

50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO.	2.	3. PB90-259920
4. Title and Subtitle: TRIALLATE: Decision Document			5. Report Date: November 1980
			6.
7. Author(s): EPA, OPP, REGISTRATION DIVISION			8. Performing Organization Rept. No. 540/09-90-101
9. Performing Organization Name and Address: ENVIRONMENTAL PROTECTION AGENCY OFFICE OF PESTICIDE PROGRAMS WASHINGTON, D.C. 20460			10. Project/Task/Work Unit No. 11. Contract(C) or Grant(G) No. (C) (G)
12. Sponsoring Organization Name and Address: SAME AS #9			13. Type of Report & Period Covered 14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

→ to p. 1

17. Document Analysis a. Descriptors

PESTICIDES, STANDARDS, REGULATIONS, MANUFACTURING, CHEMISTRY, TOXICOLOGY, RESIDUES, ECOLOGY, PATH OF POLLUTANTS

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement	19. Security Class (This Report)	21. No. of Pages
PUBLICLY AVAILABLE	UNCLASSIFIED	45
	20. Security Class (This Page) UNCLASSIFIED	22. Price

(See ANSI-Z39.18)

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

Table of Contents

Section		Page
I.	Introduction	1
II.	General Information	2
	A. Chemical Identity	2
	B. Chemistry	2
	C. Pesticide Formulations	2
	D. Production	2
	E. Registered Uses	5
	F. Fate in the Environment: Soil	5
	G. Fate in the Environment: Plants	8
III.	Exposure and Mammalian Metabolism	10
	A. Tolerances	10
	B. Avenues of Human Exposure	11
	1. Dietary Exposure	11
	2. Applicator (Dermal and Respiratory) Exposure	12
	C. Mammalian Metabolism	14
IV.	Triallate as a Potential RPAR Candidate	16
	A. Introduction	16
	B. Evidence Pertaining to Oncogenicity	19
	C. Evidence Pertaining to Mutagenicity	20
	D. Evidence Pertaining to Teratogenic and Fetotoxic Effects	24
	E. Evidence Pertaining to Neurotoxicity	27
V.	Conclusions and Recommendations	29
	A. Oncogenicity	29
	B. Mutagenicity	30
	C. Teratogenic and Fetotoxic Effects	31
	D. Neurotoxicity	32
	E. Metabolic Effects	32
VI.	Bibliography	33
APPENDIX:	EPA Policy on IBT Generated Data	A-1

List of Tables

		Page
1.	Comparison of Diallate and Triallate	3
2.	Micrograms of Triallate Recovered From Soil-Water Mixtures in a Closed System	7
3.	Worst-Case Dietary Exposure to Triallate	12
4.	Exposure and Total Body Doses--Applicators	13
5.	Pivotal Triallate IBT Studies	18
6.	Summary of Studies Pertaining to the Mutagenicity of Triallate	21

I. INTRODUCTION

Triallate is a pre-emergent selective herbicide used to control wild oats in small grains (barley and wheat) and in field crops (lentils and peas). Triallate was referred to the Special Pesticide Review Division as a possible candidate for the Rebuttable Presumption Against Registration (RPAR) process because of its structural similarity to diallate, which had been found to induce oncogenic effects in test animals.[1/] Structurally, triallate and diallate differ only in that triallate possesses one additional chlorine atom, and as a consequence of this basic structural difference, triallate lacks the cis and trans isomers, which are part of the structural formula of diallate. Given the similar use patterns and chemical properties of the two herbicides, the Agency felt that a review of triallate data to determine adverse effects was warranted.

This document reports the results of the Agency's review of currently available evidence concerning the potential effects of triallate. It contains six parts. Part I is this introduction. Part II presents general information about triallate. Part III evaluates available exposure data on triallate. Part IV discusses the hazard evidence for considering triallate as an RPAR candidate. The conclusions and recommendations given in Section V are based on considerations of exposure as well as toxicological evidence. Part VI is a bibliographical listing of studies cited.

1/ The Agency issued a notice of Rebuttable Presumption Against Registration (RPAR) for diallate on May 31, 1977. (See Fed. Reg. 42 (104): 27669-27674 [May 31, 1977].) The Agency presumed against diallate on the basis of oncogenic effects in test animals and also requested additional information on the following possible adverse effects: mutagenicity, neurotoxicity, and reproductive effects. In Diallate: Position Document 2/3 the Agency maintained that the presumption of oncogenicity was unrebutted and that a presumption based on mutagenicity was also warranted. (See Fed. Reg. 45 (112): 38437-38440 [June 9, 1980].)

II. GENERAL INFORMATION

A. Chemical Identity

Triallate was patented by the Monsanto Chemical Company in July 1967 under United States Patents 3,330,643 and 3,330,821, and it is marketed under the trade names AVADEX BW® and FAR-GO®. The Chemical Abstracts Service (CAS) has assigned triallate the CAS registry number 2303-17-5 and the following name:

S-(2,3,3-trichloroallyl) diisopropylthiocarbamate.

B. Chemistry

Triallate is manufactured by the reaction of a diisopropylthiocarbamate salt with 1, 1, 1, 3-tetrachloropropene. Monsanto Company is the sole producer of technical grade triallate in the United States. The technical grade compound is 90% pure, with the remaining 10% consisting of unreacted intermediates. Triallate is an amber liquid, is soluble in most organic solvents, and is practically insoluble in water (4 ppm at 25°C). Its boiling point is 148°C, and it is volatile with a vapor pressure of 1.2×10^{-4} mm Hg. (See Table 1, which summarizes basic differences and similarities between triallate and the RPAR chemical diallate.)

C. Pesticide Formulations

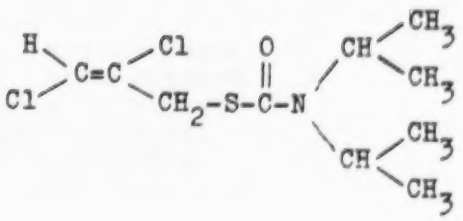
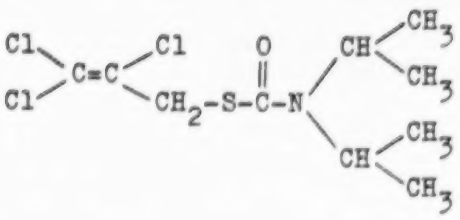
Triallate is marketed in the United States in two formulations: as a granular, and as an emulsifiable concentrate (4 pounds/gallon). The granular formulation consists of 10% active ingredient triallate and 90% inert ingredients. The emulsifiable concentrate consists of 46.3% active ingredient triallate and 53.7% inert ingredients.

D. Production

Under Section 7(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), producers and formulators of triallate must submit data on the amount of triallate which they produce or formulate each year. However, these data are classified as Confidential Business Information and are protected from disclosure to the public under Section 10 of FIFRA[2/].

2/ Data concerning production and formulation have been made available to the EPA Administrator in a confidential appendix to this report.

Table 1. Comparison of Diallate and Triallate

Diallate	Triallate
	
Formula	**Formula**
$C_{10}H_{17}Cl_2NOS$	$C_{10}H_{16}Cl_3NOS$
Formula Weight	**Formula Weight**
270.2	304.7
Solubility - Water	**Solubility - Water**
14 ppm, 25°C	4 ppm, 25°C
Vapor Pressure	**Vapor Pressure**
1.4×10^{-4} mm Hg, 25-30°C	1.2×10^{-4} mm Hg, 25-30°C
State	**State**
Amber liquid	Amber liquid
Formulations	**Formulations**
10% granular* Emulsifiable concentrate (4 lbs/gal)	10% granular Emulsifiable concentrate (4 lbs/gal.)
Registered Use Profile	**Registered Use Profile**
Pre-emergent herbicide against wild oats in sugar beets, flax, barley, lentils, peas, corn, forage legumes, potatoes, and soybeans	Pre-emergent herbicide against wild oats in wheat, barley, green peas, field dried peas, and lentils

* Granular formulation of diallate registered for use only on sugar beets

Table 1. Comparison of Diallate and Triallate (Cont.)

Diallate	Triallate
40 CFR 162.11 Risk Criteria Met or Exceeded	Areas of Concern
Oncogenicity	Oncogenicity
Mutagenicity	Mutagenicity
	Reproductive Effects
	Fetotoxic Effects
	Teratogenic Effects
	Neurotoxicity
Other Areas of Concern	
Neurotoxic Effects	
Reproductive Effects	
Fetotoxic Effects	
Teratogenic Effects	

E. Registered Uses

At the present time, two registrants hold six registrations for the use of triallate.

Triallate was first registered by Monsanto on February 15, 1962 (EPA Reg. No. 524-124). This registration permitted the use of triallate on spring and durum wheat and barley for pre-emergence control of wild oats. Triallate's use was later extended to include dried field peas (on February 20, 1963), and on winter wheat, green peas, and lentils (May 8, 1972). Emulsifiable concentrate triallate is now registered to control wild oats in winter wheat, spring and durum wheat, barley, green peas, field dried peas, and lentils. The granular formulation is registered for use only to control wild oats in wheat and barley. As a granular formulation or as an emulsifiable concentrate, triallate is applied either in the spring or in the fall (after harvest).

According to label directions, granular triallate must be applied with 1) a ground broadcast applicator, such as a grass seed attachment, 2) a specially designed ground applicator, or 3) an airplane capable of applying small quantities of granules evenly. In connection with ground equipment, the label emphasizes the importance of proper calibration so that even distribution is achieved and neither too little nor too much of the product is applied. In connection with aerial applications, attachments designed for applying low volumes of granules are specifically required. With respect to field preparation, the label directs that all deep tillage by cultivation, or double disc implements, must be completed prior to application. The granular formulation should be incorporated within 48 hours of application.

As an emulsifiable concentrate, triallate is sprayed before seeding for selected crops and incorporated with a disk-type implement to a depth of approximately two inches, followed by two harrowings. The concentrate should be incorporated into the soil on the day of application. Boom sprayers are recommended for spraying the emulsifiable concentrate, rather than other application procedures. If applied to certain crops after planting, the herbicide is sprayed onto the soil surface and then shallowly incorporated into a layer above the level of seed placement. The herbicide is incorporated by harrowing twice with a tandem disc or other implement.

F. Fate in Environment: Soil

Triallate appears to be degraded in soil, primarily through microbiological action. This degradation process has been demonstrated in a study in which triallate degraded

more rapidly in moist, non-sterile soils than in moist, sterile soils (Cullimore and Smith, 1972). After 16 weeks, less than 5% of the triallate was lost from moist, sterile clay and loam, whereas 65% and 75% were lost from moist, non-sterile clay and loam (Cullimore and Smith, 1972).

Available studies do not indicate that triallate is likely to migrate through the soil. A study has shown that triallate is well adsorbed to a variety of dry plains soils, including clays and loams (Smith, 1970). However, in situations where there is an excess of moisture, triallate will desorb from clay soils, but not from organic soils (Grover, 1974). The crops for which triallate is used (wheat, barley, green peas, field dried peas, and lentils) are grown in a wide variety of soils, though organic soils are generally preferred over clay soils. Therefore, significant triallate desorption as a result of excess moisture is not expected.

Triallate's volatility has been demonstrated in a closed system (Hance et al., 1973) using composite soils typical of those found in the areas where the chemical is used. When different formulations and soil types were used, the volatility of triallate was found to increase as the water content for each soil type increased. A maximum of 4% loss by volatility in sandy soils, and 2% in clay soils, occurred with the liquid formulation. The granular formulation was found to have the lowest volatility. Detailed results from this study are shown in Table 2. The findings of Hance et al. (1973) correspond with current label directions, which caution users against applying the herbicide immediately before or after rain, since loss of efficacy due to volatility occurs under these conditions.

Residues of triallate have been found to persist in the soil from one growing season to the next. Data from the Canadian prairie provinces indicate a carryover of about 15% to 20% in a 5-month growing season (Smith, 1970). However, since triallate's persistence is to some extent related to climatic temperature, the compound may be less persistent in the warmer soil temperatures of the United States (Smith, 1969).

A report was submitted to the Agency in support of triallate's registration (Monsanto, 1975 [Report # 524-124]) which contained results of laboratory and field tests concerning the fate of the herbicide in soils. Studies were included which pertained to dissipation, degradation, and metabolism of triallate in soil, as were leaching and runoff studies. The stated purpose of the studies pertaining to the dissipation, degradation, and metabolism of triallate in soils was to determine the rate of dissipation and the mechanism of degradation. The

Table 2. Micrograms of Triallate Recovered from Soil-Water Mixtures in a Closed System

Triallate Added (micrograms)	Water Content	Micrograms of Triallate Recovered: Sandy Soil 10	Sandy Soil 50	Sandy Soil 100	Clay Soil 10	Clay Soil 50	Clay Soil 100
Unformulated (a)							
	2%	0.10	0.34	0.52	0.02	0.14	0.20
	6%	0.20	0.80	2.00	0.04	0.34	0.50
	(b)	0.30	1.35	2.35	0.20	0.80	1.56
Liquid formulation							
	2%	0.05	0.38	0.88	0.02	0.25	0.32
	6%	0.30	1.18	2.62	0.08	0.35	0.58
	(b)	0.40	1.85	3.60 (c)	0.15	1.10	1.90 (
Granular formulation							
	2%	<.02	<.02	<.02	<.02	<.02	<.02
	6%	0.20	0.54	0.92	0.08	0.30	0.30
	(b)	0.24	1.00	1.70	0.02	0.32	0.55

(a) Technical Grade

(b) Field capacity soil condition (moisture content) that exists 24 hours after the water supply is shut off (i.e., stops raining, turn-off irrigation water, etc.).

(c) Highest volatility rounded to 4.0% in saturated sandy soils.

(d) Highest volatility rounded to 2.0% in saturated clay soils.

Source: Hance et al. (1973).

Agency's review of these studies, however, pointed out a number of deficiences which undermine the usefulness of the experiments. Problems were noted, for example, in the design of the experiments in that these laboratory studies used 5 g of soil suspended in 100 ml of water. Since the report states that the degradation rate of triallate is moisture-dependent, these laboratory conditions represent a poor model for actual field behavior. Mechanical problems were also encountered in connection with the limited water solubility of triallate. In addition, presentation was inadequate to the extent that comparison of data from various cultures was difficult, and the reports were not internally consistent. In view of the deficiencies outlined above, the Agency's judgment is that although Monsanto's conclusion that triallate is "biologically degraded by soil microflora as evidenced by the degradation of carbon-14 labeled AVADEX BW to 14-CO_2" may be correct, it is not substantiated by the data submitted (Severn, 1977).

The leaching studies were done by a generally acceptable procedure, the Helling soil TLC technique, which yielded a comparison of the mobility of triallate in three different types of agricultural soils. The types of soils tested were Chillum soil, Hagerstown silty clay loam, and Lakeland clay loam (Selim, 1978). In terms of Helling's mobility classifications, triallate exhibited a mobility typical of Class II pesticides (pesticides which move 10% - 35% compared to water in the same type of soil). The conclusion of Monsanto Co. (1975), that triallate "adsorbs to soil and does not pose a threat to the environment due to leaching" is in the Agency's judgment probably correct. The Agency points out, however, that although triallate is in general used in areas where the water table is relatively low, triallate's entry into the water would be possible in areas of heavy rainfall where the water table is near the surface.

Runoff studies were done on a small, inclined laboratory box filled with triallate-treated soils, using sprinklers to simulate rainfall. Only 50 ml samples of runoff were collected, and in the Agency's judgment, this amount is much too small to evaluate runoff potential. Runoff water and sediment contained 0.004-0.09% of the applied radioactivity. In view of the inadequate size of the samples collected, Monsanto's conclusion, that "under field conditions contamination of non-target land and aquatic areas will be insignificant," cannot be regarded as substantiated by this particular experiment (Severn, 1977).

G. Fate in the Environment: Plants

A review of the available data indicates that triallate does not bioaccumulate in plants, and the ability of plants to degrade triallate lessens the potential for bioaccumulation in soils. Some plants apparently absorb triallate (a pre-emergent herbicide), or its metabolites and degradation products, from the soil, as indicated in connection with wheat and peas in several studies submitted by Monsanto in support of registration (PP 0F0944). Specifically, these studies indicate that when soil is treated with radiolabeled triallate, radioactivity is detected in plant extracts. Radioactivity is found in the soluble protein, lipids, soluble carbohydrates, insoluble cellulose and lignin fractions, as well as in CO_2 captured above the plant. In wheat and peas, the soluble fractions were found to contain, respectively, 60% and 82%, and the insoluble fractions, 31% and 11% of the radioactive labeling. Collectively these studies also indicate that in view of the detection of a small amount of the radioactivity (<5%) in the released CO_2 in both crops (wheat and peas), not only absorption, but complete metabolism of triallate by the plant may take place (Monsanto Chemical Co., PP 0F0944).

III. EXPOSURE AND MAMMALIAN METABOLISM

A. Tolerances

In order for a pesticide to be sold and used in the production of a crop, the pesticide must not only be registered for the particular use under FIFRA, but must have a tolerance or an exemption from a tolerance under the Federal Food, Drug and Cosmetic Act (FFDCA) for each individual crop on which it will be used. Under Section 402 of the FFDCA, a raw agricultural commodity or a processed food or feed which contains a pesticide residue is considered "adulterated" unless a tolerance (maximum allowable limit of pesticide residue), and exemption from a tolerance, or a food additive regulation has been established for the pesticide in question. The authority for establishing tolerances and exemption from tolerances for residues of pesticide chemicals on raw agricultural commodities, and food additive regulations allowing pesticide residues in processed food, is found in Section 408 (raw agricultural commodities) and 409 (processed food) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. Section 346(a), 348. In 1970, pursuant to the Reorganization Plan No. 3 of 1970, 84 Stat. 3086, the authority for establishing tolerances and exemptions from tolerances under Sections 408 and 409 of the FFDCA was transferred from the Food and Drug Administration to the Administrator of EPA.

From the mid-fifties to the mid-sixties, tolerances were established "at zero level" if data showed that no detectable residues were present in the treated crop at the time of harvest. Triallate was originally registered (in 1962) in conjunction with the establishment of a zero tolerance under the "no residue-zero tolerance" concept.

In 1965, however, the National Research Council of the National Academy of Sciences recommended that the "no residue-zero tolerance" concept be abandoned because, as applied in the registration and regulation of pesticides, the concept had become scientifically and administratively outmoded and untenable. Among the specific reasons cited by the Council were that analytical methodology had improved, and that small levels of pesticide residues had thereby become detectable (Pesticide Residues Committee Report on "No Residue" and "Zero Tolerance," NAS-NRC, June 1965). At the same time, the Council also recommended that pesticides previously registered under the "no residue" concept be registered on the basis of "negligible residue" tolerances.[3/]

3/ In 40 CFR 180.1 (k)(1) the term "negligible residue" is defined as "any amount of a pesticide chemical remaining in or on a raw agricultural commodity or group of raw agricultural commodities that would result in a daily intake regarded as toxicologically insignificant on the basis of
(Cont'd on next page)

The "no residue-zero tolerance" concept applied to all pesticides, including triallate, until 1966. In 1966, the USDA began to phase out this concept as a working policy (Fed. Reg. 31(71):5723-5725 [April 13, 1966]).[4/] Registrants of pesticide products with a "no residue-zero tolerance" classification were given--through a series of 1-year extensions--until 1971 to convert the "no residue" tolerances to finite tolerances.

In 1970, Monsanto Chemical Company petitioned for a finite tolerance of 0.05 ppm in or on the following raw agricultural commodities: grain and straw of barley and wheat, lentils and lentil forage and hay, and peas and pea forage and hay (PP OF0944). The petition was granted, and tolerances for triallate were set at 0.05 ppm in the above commodities (40 CFR 180.314). The limit of detection of triallate by chemical analytical methods was .02 ppm at that time.

B. Avenues of Human Exposure

The Agency has identified human populations exposed to triallate and examined the type and extent of their exposure. Three avenues of exposure are at issue: dietary (oral), dermal, and respiratory. Dietary exposure as a result of triallate residues on food affects the general population, including pesticide applicators. In addition, applicators can be subject to dermal and respiratory exposure to triallate during mixing and loading operations, during application, and during re-entry into treated fields for purposes of incorporating the herbicide into the soil.

1. Dietary Exposure: Established tolerances provide a basis for assessing theoretical maximum ("worst case") residue levels in or on various agricultural products at the time of harvest. Tolerances for triallate have been set at 0.05 ppm (negligible residue) in or on grain and straw of barley and wheat, lentils and lentil forage and hay, and peas and pea forage and hay (40 CFR 180.314 and

---

3. (Cont'd) scientific judgment of adequate safety data. Ordinarily this will add to the diet an amount which will be less than 1/2,000th of the amount that has been demonstrated to have no effect from feeding studies on the most sensitive animal species tested. Such toxicity studies shall usually include at least 90-day feeding studies in two species of mammals."

4/ Pesticide registration and tolerance activities conducted by the USDA were transferred to the Environmental Protection Agency under Reorganization Act No. 3, December 3, 1970.

Subsection III. A above). Assuming that triallate is always present at tolerance levels in wheat, barley, and peas, dietary intake by the general population is nonetheless expected to be low (0.16 ug/kg/day for a 60-kg person). Table 3 below shows average daily consumption of these items and consequent daily intake based on tolerances.[5/]

Table 3. Worst-Case Dietary Exposure to Triallate

Items	Daily Consumption In Grams	Tolerance Level (ppm)	Total Daily Intake of Triallate
Wheat	184	0.05	9.2 ug
Barley	1.5	0.05	0.1 ug
Peas	13.2	0.05	0.7 ug
			Total Intake 0.16* (ug/kg/day)

* Assuming a 60-kg person

2. Applicator (Dermal and Respiratory) Exposure

The Agency is aware of two studies, Voytenko et al. (1972) and Arras et al. (1980) which have measured exposure to triallate during application. Because the information provided to the Agency in connection with the Voytenko study is incomplete (the rate and duration of application are not specified) the Agency has calculated exposure and total body doses to applicators (excluding dietary exposure) to triallate on the basis of the Arras et al. (Monsanto) study.

In the study performed by Arras et al., triallate was applied as an emulsifiable concentrate on six plots, and as a granular formulation on three plots. The emulsifiable concentrate was applied with a spray harrow on three plots, and with a boom spray on three plots at an application rate of 1 pound active ingredient per acre. The granular formulation was applied at a rate of 1.5 pounds active ingredient per acre on two fields, and at 1.35 pounds active ingredient per acre on one field. Following standard application practice, a second incorporation into the soil was made.

5/ Source: Mittelman (1978).

The calculations of applicator exposure made by the Agency, as shown in Table 4, are based on the following assumptions:6/

a. For respiratory exposure, maximum values were used in calculations, except for the one anomalous inhalation value obtained downwind during a tank fill and mix on an excessively windy day.

b. For dermal exposure, average values obtained for the forehead, back, and chest were used in calculations (except for one anomalous value detained for the chest).

c. An applicator weighs 60 kg.

d. Applicators follow label instructions and wear gloves and goggles.

e. Applicators' arms are covered since triallate is applied in cool weather. Therefore only the face and neck are exposed. The exposed skin area is 910 cm^2.

f. The average-size field is 100 acres, and average application time is 8.3 hours.

g. Applicators' breathing rate is 1.8 m^3 per hour.

h. One hundred percent of the inhaled material is retained.

i. The rate of dermal absorption is 10% for emulsifiable concentrate formulations and 1% for granular formulations.

As Table 4 shows, the Agency has calculated exposure and absorbed body doses for applicators working with both formulations of triallate (emulsifiable concentrate and granular). An applicator working with the emulsifiable concentrate formulation would be subject to 1) an estimated body dose of 5.6 ug/kg of body weight per day during tank fill and application procedures (day 1), and 2) an additional estimated body dose of 2.5 ug/kg/day during the process of incorporating the herbicide into the soil (day 2). An applicator working with the granular formulation would be

---

6/ Source: Jensen (1980)

Table 4. Exposure and Total Body Doses--Applicators[a/]

Formulation	Day	Task	Dermal Exposure (ug/kg/day)[b/]	Total Dermal Exposure (ug/kg/day)	Assumed Dermal Absorption Rate	Dermal Body Dose (ug/kg/day)	Respiratory Exposure (ug/kg/day)	Total Respiratory Exposure (ug/kg/day)	Assumed Respiratory Absorption Rate	Respiratory Body Dose (ug/kg/day)	Total Body Dose (Dermal & Respiratory) (ug/kg/day)	
Emulsifiable Concentrate	1	Tank fill	13.40		10%	1.8	0.073					
	1	Application	4.40	17.8[c/]			3.785	3.858[c/]	100%	3.8	5.6	(Day 1- E.C.)
Emulsifiable Concentrate	2	Incorporation	3.40	3.4	10%	0.3	2.191	2.191	100%	2.2	2.5	(Day 2- E.C.)
Granular	1	Hopper fill	31.30				0.912					
	1	Application	4.98	36.3[d/]	1%	0.4	1.843	2.755[d/]	100%	2.7	3.1	(Day 1- Granular)
Granular	2	Incorporation	2.90	2.9	1%	0.03	1.743	1.743	100%	1.7	1.8	(Day 2- Granular)

a/ Source: Jensen (1980)
b/ Applicator body weight is assumed to be 60 kg
c/ Tank fill and application
d/ Hopper fill and application

subject to 1) an estimated body dose of 3.1 ug/kg/day during hopper fill and application procedures (day 1), and 2) an additional estimated body dose of 1.8 ug/kg/day during the process of incorporating triallate into the soil (day 2). In sum, applicator exposure appears to be very low.

C. Mammalian Metabolism

When tolerances for negligible residues were established for triallate, the USDA did not require animal metabolism studies. This USDA policy was based on the assumption that the amount of the residue was sufficiently limited that it was considered to be of little or no toxicological significance (USDA, 1968). Requirements for animal metabolism studies have been established by the EPA, however, as part of its requirements for registration of pesticides, and the Proposed Guidelines for Registering Pesticides in the U.S. 40 CFR 163.85-1 (Fed. Reg. 43 (163):37394-37396 [August 22, 1978]) contain detailed protocols for testing pesticide chemicals in specified mammalian species. As stated in the Proposed Guidelines, general metabolism studies are required for the following major purposes:

"(1) To identify and, to the extent possible, quantify significant metabolites;

(2) To determine any possible accumulation and/or bioretention of the test substance and/or metabolites;

(3) To determine pesticide absorption as a function of dose;

(4) To characterize route(s) and rate(s) of pesticide excretion;

(5) To relate pesticide absorption to the duration of exposure of the animal; and

(6) To obtain an estimate of binding of the test substance and/or its metabolites by target macromolecules in potential target organs."

Animal metabolism studies on triallate remain to be submitted to the Agency. (This data gap is addressed in Section V, "Conclusions and Recommendations," Subsection V.E.)

IV. TRIALLATE AS A POTENTIAL RPAR CANDIDATE

A. Introduction

Section 3(a) of FIFRA requires all pesticide products to be registered by the Administrator of EPA before they may be sold or distributed. Section 6(b) of FIFRA authorizes the Administrator to issue a notice of intent to cancel the registration of a pesticide or to change its classification if it appears that the pesticide or its labeling "does not comply with the provisions of [FIFRA] or, when used in accordance with widespread and commonly recognized practice, generally causes unreasonable adverse effects on the environment." Thus the Administrator must cancel the registration of a pesticide whenever he or she determines that it no longer satisfies the statutory standard for registration, which requires, among other things, that the pesticide not cause "unreasonable adverse effects on the environment" [Section 3(c)(5) of FIFRA]. These "unreasonable adverse effects" are defined in Section 2(bb) of FIFRA to include "any unreasonable adverse effects to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide."

The Agency created the RPAR process to facilitate the identification of pesticide uses which may not satisfy the statutory standard for registration and to provide a public, informal procedure for the gathering and evaluation of information about the risks and benefits of these uses. The regulations governing the RPAR process are set forth at 40 CFR 162.11. In broad summary, these regulations set forth certain criteria of risk and provide that an RPAR shall arise against a pesticide if the Agency determines that the ingredient(s), metabolite(s), or degradation products(s) of the pesticide in question meet or exceed any of these risk criteria.

In administering the RPAR process, the Agency adheres to the standard for initiating the RPAR process established by Section 3(c)(8), one of the 1978 Amendments to FIFRA, which provides that the Agency may not start an RPAR unless it has "a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment". In determining whether a particular pesticide raises "prudent concerns", the Agency examines the degree of toxicity of the pesticide, as well as the likelihood of human and environmental exposure. The Agency applies this approach to all its risk triggers, including oncogenicity and mutagenicity triggers which do not on their face take exposure into account. This approach allows the Agency to avoid the burdensome consequences of an RPAR proceeding in those situations in which the uses of the pesticide at current levels of exposure does not pose an unreasonable risk to man or the environment.

Where the Agency publishes a notice indicating that an RPAR has arisen the 40 CFR 162.11 regulations require that an opportunity then be provided for registrants, applicants, and interested persons to submit evidence to rebut the presumption, or evidence relating to the economic, social, and environmental benefits for any use of the pesticide. If the presumptions of risk are not rebutted, the evidence on the benefits of the pesticide is evaluated and considered along with the information on the competing risks. The Agency then analyzes various methods of reducing the amount of risk from the pesticide together with their costs and determines whether the pesticide can be regulated so that the benefits of continued use outweigh the competing risks. If measures short of cancellation cannot reduce the risks associated with any given use of the pesticide to a level which is outweighed by benefits, the use in question must be cancelled.

To determine whether triallate might pose a hazard warranting the continuation of a rebuttable presumption, the Agency has reviewed all currently available data on the potential effects of the herbicide and, where appropriate, has taken considerations of exposure into account. The potential effects which warrant concern, and which are at issue in this review, are oncogenicity, mutagenicity, teratogenicity and fetotoxicity, and neurotoxicity.

By way of introduction to a discussion of triallate as an RPAR candidate, it is necessary to address the following considerations regarding the toxicological data base on which existing triallate registrations and tolerances were established. In 1977, the EPA Office of Pesticide Programs established a Toxicology Data Audit Program (TDAP), the function of which was to assure the reliability and integrity of data supplied to the Agency by pesticide manufacturers for purposes of supporting pesticide registrations and tolerances. Industrial Bio-Test Laboratories (IBT), which performed a large volume of testing used by the Agency in its regulatory decision-making concerning numerous chemicals (including triallate), was one of the initial laboratories audited jointly by the EPA and the Food and Drug Administration. During the audit at IBT, a number of questionable scientific practices were documented, and this led the Agency to require supporting evidence (raw data) for purposes of reevaluating all IBT studies used in support of pesticide registrations and tolerances. (See Appendix for an updated policy statement, issued by the Agency on July 29, 1980, on IBT-generated data.)

The workload of this reevaluation/validation program was shared with the Canadian government in cases wherein chemicals were registered in the U.S. and in Canada on identical data bases. Triallate was one of these chemicals, and the Canadian Government conducted the evaluation of the triallate data base. A number of the studies reviewed lacked complete protocols and/or supportive data.

Table 5 lists those five IBT studies which are pivotal in this review of triallate as a potential RPAR candidate, together with the results of the Canadian government/TDAP audit. The following subsections proceed with a summary review and evaluation of currently available toxicological evidence, including IBT studies, concerning triallate. Considerations of exposure are taken into account as appropriate in the Agency's evaluation of the potential hazards of triallate under current use patterns. Conclusions and recommendations arising from this review of the herbicide as a potential RPAR candidate are summarized in Section V.

B. Evidence Pertaining to Oncogenicity

40 CFR 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredients(s), metabolite(s), or degradation product(s) "induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalational, or dermal exposure." As described in the Proposed Guidelines for Registering Pesticides in the U.S., 40 CFR 163.83-1,-2 (Fed. Reg. 43 (163):37346-37347 [August 22, 1978]), oncogenicity testing "focuses on the detection of malignant and benign tumors and preneoplastic lesions" in at least one mammalian species. The species shall normally be a generally recognized species of laboratory rat. Dosing should begin as soon as possible after weaning and acclimation and in any case before the animals are 6 weeks old. Dosing should continue for a lifetime or, alternatively, for a pre-determined time span from early adulthood to past maturity, depending on the animal's life span.

The single available study for determining the oncogenic potential of triallate is a 2-year feeding study in Charles River albino rats performed by IBT for Monsanto Company (IBT No. 622-05251 [Calandra, 1976, 1977 (with addendum)]). Male and female rats (50 in each group) were fed 0, 50, 100, or 200 ppm of AVADEX BW (triallate) technical in dry, pulverized Purina Chow for 24 1/2 months. Control rats were the same as those used in a parallel diallate study. Food consumption and body weights were recorded, as were hematology, selected blood chemistries, and urinalyses at periodic intervals. On all rats killed and on all rats found dead except for advanced autolysis, complete gross necropsies were reportedly conducted, and terminal weights were taken of brain, gonads, heart, kidney, and spleen. Detailed histopathological examinations were done on "selected animals sacrificed." All neoplasms and tissues with suspected "neoplastic lesions" were studied. According to food consumption measurements, the amount of food eaten by test animals was similar to that of controls, and there was no statistically significant difference in mortality between treated and control groups.

Table 5. Pivotal Triallate IBT Studies

Type of Study	IBT No.	Status	Remarks
Chronic Oral—Rat (with Addendum)	622-05251	Invalid	Valid as an oncogenic screen test
Mutagenicity—Mouse	622-05253	Valid	
Neurotoxicity—Chicken (with Addendum)	8580-09120	Valid	
Neurotoxicity—Chicken	8580-10814	Provisionally Invalid	Reports not signed by responsible IBT staff
Teratogenicity—Rabbit	651-05255	Invalid	No raw data submitted

Upon reviewing this study, the EPA Carcinogen Assessment Group pointed out a number of deficiencies, including failure to section all tissues routinely and failure to conduct histopathological examinations on all animals sacrificed "in extremis" (Albert, 1977; 1979). Taking these deficiences into account, however, the CAG was able to conclude that "the tumor data did not indicate a statistically significant increase of total tumors or of tumors by anatomical site in either the treated males or females relative to their respective controls." The CAG recommended that an additional oncogenicity study in mice be conducted (Anderson, 1977).

Dr. I. N. Dubin of the Medical College of Pennsylvania reviewed for the CAG all of the available slides from all animals in the control group and the 100 ppm dose group (which showed the highest tumor incidence). According to Dr. Dubin's report, the only tumor incidence which might be considered statistically significant ($p<.01$) involved pituitary chromophobe adenomas in female rats (9/22 control versus 13/15 treated). Dr. Dubin pointed out, however, that because this type of tumor has a high spontaneous occurrence, the increased incidence noted may not be biologically significant, and his overall conclusion was that triallate did not produce a carcinogenic effect in this study (Dubin, 1977).

Subsequent to the CAG review, this 2-year feeding study was subject to audit by the Canadian government in conjunction with the EPA Toxicology Data Audit Program. As result of this audit, the study was pronounced valid only as an oncogenic screening test but otherwise invalid for risk assessment purposes. This determination was made on the basis of deficiencies in experimental design (Auerbach, 1979). Taking into account the limited usefulness of this study as an oncogenic screening test only, the Agency regards the current data base as inadequate to satisfy registration requirements but concludes that no rebuttable presumption against triallate is warranted on the basis of oncogenicity at this time. (See Section V, "Conclusions and Recommendations," Subsection V.A.)

C. Evidence Pertaining to Mutagenicity

40 CFR 162.11(a)(3)(ii)(A) states that "a rebuttable presumption shall arise if a pesticide's ingredient(s) metabolite(s), or degradation product(s)...induces mutagenic effects, as determined by multitest evidence." Section 162.3(y) defines mutagenicity as "the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations." Mutagenic chemicals are recognized as posing a potential risk to human health because of their ability to cause heritable changes in genes and chromosomes. Such

germline changes can, for example, lead to birth defects or to the accumulation of deleterious mutations in the human gene pool. In addition, somatic mutations may be involved in the etiology of cancer.

To determine whether or not triallate might pose a mutagenic hazard warranting a rebuttable presumption, the Agency has reviewed available data to assess the mutagenic potential of the compound. (See Table 6, which summarizes studies pertaining to the mutagenicity of triallate.)

In a dominant lethal test performed by IBT (IBT No. 622-05253 [Calandra, 1974a]), Charles River strain albino mice were administered single intraperitoneal injections of either 200 or 400 mg/kg triallate. Negative results were reported. Battelle Laboratories reviewed this study and despite minor objections to the methodology employed, concurred that triallate did not appear to be mutagenic in the dominant lethal test (Freudenthal et al., 1977). A second review by an Agency scientist (Pertel, 1977) likewise confirmed the negative findings of IBT regarding the dominant lethal assay but pointed out that the dominant lethal is a relatively insensitive test capable of detecting only the most potent mutagens. Subsequently, the negative results of the IBT dominant lethal test in mice were declared valid following a review of the raw data by the Canadian government in conjunction with EPA's Toxicology Data Audit Program.

Triallate has subsequently been tested in the *in vitro* mouse lymphoma assay, and conflicting results have been reported. Brusick (1977b) reported that triallate did not cause forward mutations at the TK locus of strain L5178Y cells. More recently, however, Mitchell (1980) conducted a similar test and reported that triallate was positive for forward mutations at the TK locus of strain L5178Y cells. The Agency has reviewed these studies and points out that the conflict in evidence can be resolved only if additional studies are conducted.

Triallate has also been tested in the standard battery of bacterial *Salmonella typhimurium* strains, both with and without metabolic activation (Ames assay) by a number of researchers including Andersen et al. (1972), Sikka and Florczyk (1978 [pre-publication copy reviewed by the Agency in 1977]), Brusick (1977a), De Lorenzo et al. (1978), and Simmon et al. (1978). Triallate has also been tested in the WP2 strain of *E. coli* (Simmon et al., 1978). Triallate has likewise been tested for mutagenicity using the yeast *Saccharomyces cerevisiae*. Using *Saccharomyces cerevisiae* strain D3, Simmon et al. (1978) reported positive results for mitotic recombinations in that strain. However, Brusick (1977a) reported negative results in *Saccharomyces cerevisiae* strain D4.

Table 6. Summary of Studies Pertaining to the Mutagenicity of Triallate

Test Species	Author, Date	Results Reported	Agency Comments
Albino Mice	Calandra, 1974a (IBT Study)	Dominant lethal test - triallate does not cause heritable lethal mutagenic effects	Pronounced valid following audit by the Canadian government in conjunction with EPA's TDAP
Bacteria S. typhimurium with metabolic activation	Sikka & Florczyk, 1978	Positive for base pair conversions in strains TA 100, TA 1535	
Bacteria S. typhimurium with no metabolic activation	Sikka & Florczyk, 1978	Negative for base pair conversions in strains TA 100, TA 1535, TA 98, TA 1538	
Bacteria S. typhimurium with metabolic activation	DeLorenzo et al., 1978	Positive for base pair conversions	
Bacteria S. typhimurium (No activation)	Anderson et al., 1972	Negative for base pair conversions	
Bacteria S. typhimurium with activation	Brusick, 1977	Positive for base pair conversions	
Bacteria S. typhimurium with activation	Simmon et al., 1978	Positive for base pair conversions	
Bacteria E.coli strain WP2	Simmon et al., 1978	Negative for base pair conversions	

Table 6. Summary of Studies Pertaining to the Mutagenicity of Triallate (Cont.)

Test Species	Author, Date	Results Reported	Agency Review
Yeast Saccharomyces Cerevisiae	Simmon et al., 1978	Positive for mitotic recombinations in strain D3	
Yeast Saccharomyces Cerevisiae	Brusick, 1977	Negative for gene conversion in strain D4	
Mouse lymphoma cells LY5178Y	Brusick, 1977	Negative for forward mutations at the TK $^{+}/_{-}$ locus	
Mouse lymphoma cells LY5178Y	Mitchell, 1980	Positive for forward mutations at the TK $^{+}/_{-}$ locus	
Bacteria S. typhimurium	Carere et al., 1978b	Positive for base pair conversions in strain TA 1535	Under Agency Review
Bacteria Streptomyces coelicolor	Carere et al., 1978b	Positive for base pair conversions	Under Agency Review
Yeast Aspergillus sp.	Carere et al., 1978a	Positive mutagenic effect	Under Agency Review
Yeast Aspergillus sp.	Bignami et al., 1977	Positive mutagenic effect	Under Agency Review
Plant Pelargonium Zonale	Polheim et al., 1977	Positive mutagenic effect	Under Agency Review

The Agency has reviewed these bacterial and yeast tests and concludes 1) that triallate induced base-pair substitution (positive) with metabolic activation (MA) in strains TA-100 and TA-1535, 2) that strain 98 showed a "weak" positive (only in the presence of MA), 3) that the WP2 strain of E. coli showed a negative response, and 4) that evidence of triallate's ability to enhance mitotic recombination in yeast is suggestive but not conclusive (Mauer, 1980).

In addition to the studies discussed above, the work of Carere et al. (1978) and Polheim et al. (1977) is currently under review by the Agency. Carere et al. tested triallate in Salmonella typhimurium and Streptomyces coelicolor and reported the chemical to be a "powerful mutagen" in strain TA1535 and positive for base pair conversions in S. coelicolor. Carere et al. also tested triallate for mutagenicity using the yeast Aspergillus sp. and reported a positive mutagenic effect. Polheim et al. (1977) reported that triallate showed a strong mutagenic influence in the monohaploid Pelargonium zonale, a plant.

Although the studies performed by Carere et al. (1978) and Polheim et al. (1977) remain to be evaluated by the Agency, and although reported results in similar test systems are at variance, the 40 CFR 162.11(a)(3)(ii)(B) risk criterion of "mutagenic effects, as determined by multitest evidence" has been met. Additional information is necessary, however, to determine the potential of triallate to reach the mammalian gonad, and thereby to more fully assess the potential of triallate to cause heritable effects. In view of the low level of exposure (Subsection III. B.) and the lack of data indicating a strong mutagenic potential the Agency has concluded that the potential for triallate to produce mutagenic events in humans is very low. Hence, the Agency has determined that the issuance of a rebuttable presumption against registration for triallate on the basis of mutagenicity is not warranted at this time. In essence, the Agency has made a determination in accordance with 40 CFR 162.11 (a)(4)(ii) that the RPAR concerning mutagenicity which has technically been raised has been rebutted by the exposure information available to the Agency, and that the "pesticide will not concentrate, persist or accrue to levels in man or the environment likely to result in any significant chronic adverse effects." The Agency has in effect rebutted its own presumption based on exposure. The Agency will, however, require additional tests in the area of mutagenicity to enable a better characterization of the mutagenic potential of the compound. (See Section V, "Conclusions and Recommendations" Subsections V.B. and V.E.)

E. Evidence Pertaining to Teratogenic and Fetotoxic Effects[7/]

40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation products(s)...produces any other chronic or delayed toxic effect [i.e., other than oncogenic or mutagenic effects] in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account an ample margin of safety." Currently available information pertaining to the teratogenic and fetotoxic potential of triallate is limited to a single study performed by Industrial Bio-Test Laboratories (IBT Report No. 651-05255 [Calandra, 1974b]) and submitted to the Agency by Monsanto Company. Two groups of New Zealand albino rabbits were administered triallate (AVADEX BW technical) at doses of 3 mg/kg/day and 10 mg/kg/day for 12 days during gestation. IBT reported that "no dose or test material related" fetotoxic or teratogenic effects were observed which could be attributed to treatment with triallate. A "no observable effect level" (NOEL) was not established.

This study was reviewed for the Agency by Battelle Laboratories, which noted that 1 out of 70 triallate treated fetuses displayed talipomanus (club foot), while none of the 189 control fetuses were affected and concluded 1) that depending upon the background incidence of this abnormality in albino rabbits, this observation may represent a low level of teratogenic activity, and 2) that additional testing in at least one more species would be necessary for purposes of assessing the teratogenic potential of triallate in animals. A second review of this study by an Agency scientist (Chernoff, 1977) pointed out further 1) that the number of resorption sites/100 implantation sites were greater in both experimental groups as compared to the control group, 2) that historical rather than concurrent control groups were used and no explanation for this departure from accepted practice was provided, and 3) that calculation of fetal weights on a litter basis indicates that a significant ($p<0.05$) dose-related reduction in fetal weight occurred in treated litters in both dose groups. In view of the above, Chernoff (1977) recommended that this study be repeated in the rabbit and that an additional study be conducted in another species such as the rat.

7/ A 3-generation reproduction study of triallate in rats (Industrial Bio-Test No. 623-06842) has been contracted by Monsanto Company. The Agency has as yet received data pertaining only to the F^0 (parental) generation. Because the final report has not been submitted or evaluated, the Agency cannot comment on this study at this time.

This IBT study was subsequently audited by the Canadian government in conjunction with EPA's Toxicology Data Audit Program and was pronounced not valid: "In the absence of raw data on fetal skeletal development and on internal development, the study cannot be validated" (Auerbach, 1979). A second Agency scientist (Edwards, 1979) has pointed out that although this study has been declared not valid and is inadequate for registration, it contains indications of adverse effects which must be acknowleged. More specifically, 1) a possible effect on fecundity is indicated by the reduced percent of pregnancies reported in the treated groups; 2) reduced weights of progeny at birth were noted in treated groups, and though these differences were seemingly small, they were significant at the 99% confidence level for both triallate-treated groups; and 3) a greater incidence of fetal abnormalities was found in the progeny of treated than of untreated groups. Except for reduced birth weights, all the fetal effects noted above were more extensive in the low dose group (3 mg/kg) than in the high dose group (10 mg/kg), and this irregular relationship is unexplained. Noting that both dose groups nonetheless showed indications of adverse effects, Edwards (1979) recommended that an additional teratology study be conducted according to the latest guidelines and that a NOEL be determined.

Given the deficiencies which have been pointed out in connection with this IBT test as the single available study of teratogenic and fetotoxic potential of triallate, the Agency regards the current data base as clearly inadequate to satisfy registration requirements. However, the available study by IBT (Calandra, 1974b) provides a basis on which to conduct a rough assessment of the teratogenic and fetotoxic potential of triallate.

Ordinarily, when a pesticide has been shown to produce teratogenic and/or fetotoxic effects in laboratory animals, the Agency assesses human risk by comparing the no observable effect level (NOEL), as established in animal studies, with the highest estimated daily acute exposure to humans. The ratio of the NOEL to the estimated human exposure is used to determine margins of safety. As discussed above, a NOEL was not established by Calandra (1974b), and additional testing is necessary to determine a NOEL for triallate-related teratogenic and fetotoxic effects.

In the absence of an established NOEL, the Agency has calculated a rough, preliminary estimate of human risk by comparing the lowest dose level tested (3 mg/kg body weight per day in rabbits) with the estimated daily acute exposure 1) to applicators, who represent the human population subject to the highest estimated levels of exposure (dermal,

respiratory, and dietary) to triallate, and 2) to the general public, which is subject to dietary exposure as a result of triallate residues on wheat, barley, and peas. (Refer to Subsection III.B.)

Applicators who work with the emulsifiable concentrate formulation of triallate are subject to somewhat higher levels of exposure than are applicators who work with the granular formulation. With either formulation, only one application is made per year, per field. During tank fill and application procedures involving emulsifiable concentrate triallate, an applicator is exposed to an estimated 5.6 ug/kg body weight per day in addition to an estimated 0.2 ug/kg/day as a result of dietary exposure to triallate. This represents a level of exposure (6.6 ug/kg/day) which is approximately 1/500th the level at which fetotoxic effects were observed in rabbits (3 ug/kg/day). During the process of incorporating emulsifiable concentrate triallate into the soil, an applicator is exposed to an estimated 2.7 ug/kg/day, including an estimated 0.2 ug/kg/day as a result of dietary exposure. This level of exposure is approximately 1/1100th the level of exposure at which fetotoxic effects were observed in rabbits. During hopper fill and application procedures involving granular triallate, and during the process of incorporating the granular formulation into the soil, an applicator is exposed to an estimated 3.3 and 1.9 ug/kg/day, respectively, again taking dietary exposure into account. These levels of exposure represent approximately 1/900th and 1/1500th, respectively, the level at which fetotoxic effects were observed in rabbits.

At an estimated 0.2 ug/kg/day, dietary exposure (worst-case) to the general public represents a level of exposure which is roughly 1/19,000th the level at which fetotoxic effects were observed in rabbits.

Taking into account the decidedly limited toxicological evidence presently available in the IBT test conducted by Calandra (1974b), considered together with the low levels of exposure (dermal, respiratory, and dietary) associated with triallate under current use patterns, the Agency regards the current data base as inadequate to satisfy registration requirements but concludes that no rebuttable presumption against triallate on the basis of teratogenic and fetotoxic effects is warranted at this time. (See Section V, "Conclusions and Recommendations", Subsection V.C.).

E. Evidence Pertaining to Neurotoxicity

As stated above in connection with teratogenic and fetotoxic effects, 40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation products(s)...

produces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account an ample margin of safety." A neurotoxic pesticide is defined as one which causes damage to the nervous system. Neurotoxicity is discussed in the following paragraphs 1) in terms of acute delayed neurotoxicity and 2) in terms of another type of neurotoxicity which might be associated with exposure to triallate.

As defined in the Proposed Guidelines for Registering Pesticides in the U.S., acute delayed neurotoxicity is a syndrome in which signs of nerve damage first appear several days to a few weeks after exposure to a neurotoxic pesticide. Hence the effect is termed "delayed." Delayed neurotoxicity may result in permanent paralysis. As stated in the Proposed Guidelines, "EPA's experience indicates that every compound which produces delayed neurotoxicity in any test system will also cause delayed neurotoxicity when given in a very large dose to hens under an acute regimen. [Hens are therefore the test animals of choice for delayed neurotoxicity studies.] Thus, the acute delayed neurotoxicity study would be used to identify these compounds, and if positive results are observed in the study further testing would be required" (Fed. Reg. 43 (163):37345 [August 22, 1978]).

Regarding acute delayed neurotoxicity as a possible adverse effect of exposure to triallate, two studies are available, both of which were performed by Industrial Bio-Test Laboratories (IBT Nos. 8580-09120 and 8580-10814) for Monsanto Company. In IBT study No. 8580-09120, conducted by Keplinger (1976), 10 chickens were given doses of 312 mg/kg twice daily by gavage on days 1 through 3 and on days 21 through 23. Following a review of the raw data, this study was pronounced valid by the Canadian government in conjunction with EPA's Toxicology Data Audit Program (Auerbach, 1979). The raw data were found to agree with the final report. All birds showed moderate ataxia and lethargy and general weakness of legs and wings, from which 7 of the 10 birds recovered by the end of the experiment. Only one bird reportedly showed lesions of the nervous system--the most severe effect noted in this experiment--upon histopathologic examination. Subsequent review by an Agency scientist (Edwards, 1979), however, questioned the credibility of a severe effect (neurotoxic lesions) in one hen when there were no comparable effects in nine. Marek's disease was also found in these animals.

In IBT study No. 8580-10814 (Keplinger, 1978), multiple doses (0.01, 0.02, 0.04, 0.08, 0.16, and 0.32 gram/kg) were administered to hens twice daily for two 3-day periods (days 0, 1, 2, 21, 22, and 23). (The cumulative

dose per hen was thus 0.12, 0.24, 0.48, 1.92, or 3.84 gram/kg body weight). Following an audit of the raw data by the Canadian government in conjunction with the EPA Toxicology Data Audit Program, this study was pronounced "provisionally invalid" because signatures of responsible IBT staff members were not available (Auerbach, 1979). This study was subsequently reviewed by an Agency scientist (Edwards, 1979), who pointed out 1) that no behavioral signs were found in treated animals, and 2) that focal lesions of axonal degeneration were found in one of ten birds which received 0.16 gram/kg but in none of the ten which received 0.32 gram/kg. Edwards (1979) concluded that the degeneration could not be treatment-related.

The possibility that triallate might be associated with another type of neurotoxicity has been raised by a study reported to the Agency by Monsanto Company.[8/] Rats were treated with a mixture of chemicals, one of which was triallate. Treatment resulted in symptoms including circling behavior, head tremors, and head tilt to one side. Symptoms were exacerbated by external stimulation. In addition, these symptoms were said to have been observed in quail which had been treated with triallate alone, and this suggests that the effects observed in rats were due to triallate. Because observation of the rats ceased after the end of dosing, no distinction could be made between transient effects and permanent damage, and the issue of whether or not the effects in question are persistent remains to be resolved.

With respect to acute delayed neurotoxicity as a possible adverse effect of exposure to triallate, the Agency has determined that no rebuttable presumption is warranted and that no further testing is necessary. With respect to the adverse effects seen in the rat study described above, however, appropriate neurotoxicity testing in rats is required to clarify the nature of this potential hazard and to determine a no observable effect level (NOEL). Monsanto Company has agreed to submit data to clarify this area of concern and to collaborate with the appropriate Agency scientist regarding study protocols and time frame projections. Taking all currently available evidence into account, the Agency concludes that no rebuttable presumption against triallate on the basis of neurotoxicity is warranted at this time. (See Section V, "Conclusions and Recommendations," Subsection V.D.)

8/ The results of this study were reported verbally at the EPA/Monsanto meeting of September 9, 1980, the purpose of which was to informally discuss data requirements and testing protocols. A final report of the study is not available.

V. Conclusions and Recommendations

The conclusions and recommendations arising from this review of triallate as a potential RPAR candidate are based 1) on considerations of toxicity as determined by the Agency's review and evaluation of available toxicological data, and 2) on considerations of exposure. In summary, the Agency has determined that triallate should be returned to the registration process with the stipulation that a FIFRA Section 3(c)(2)(B) action ("additional data to support existing registrations") be initiated to obtain the toxicity data necessary to fully evaluate the potential hazards of triallate. Though certain risk criteria have been met, and even though the Agency remains concerned regarding oncogenicity, mutagenicity, fetoxicity and teratogenicity, and neurotoxicity, this action is recommended because exposure to triallate is expected to be insignificant.

Upon receipt and evaluation of the necessary data, the Agency will reassess the potential hazards of triallate, taking the complete data base into account. Conclusions and recommendations regarding the specific areas of concern addressed in this review are given below.

A. Oncogenicity

The Agency has concluded that the current data base is inadequate to satisfy registration requirements. However, the available study by Industrial Bio-Test Laboratories (IBT No. 622-05251 [Calandra, 1976, 1977 (with addendum)] which is valid as an oncogenic screening test only, is considered evidence that no rebuttable presumption on the basis of oncogenicity is warranted at this time. Studies are required as specified in the Proposed Guidelines for Registering Pesticides in the U.S., 40 CFR 163.83-1 and -2 (Fed. Reg. 43(163):37346-37347 [August 22, 1978]).

B. Mutagenicity

The Office of Pesticide Programs (OPP) Working Paper on Mutagenic Risk Assessment Policy, issued in October, 1980, states that "Qualitative assessments of risk will be made based upon scientific evaluation of a chemical's behavior in various mutational test systems, knowledge of the chemical's entry into the mammalian gonad, and the expected pattern and level of exposure." In the case of triallate, conflicting test results impede a conclusive determination of the chemical's behavior in various mutational test systems. In the absence of data concerning the metabolism of triallate in mammals, moreover, it is not possible to estimate the likelihood of the chemical's entry into the mammalian gonad. This difficulty, coupled with an expected low level of exposure, results in a determination that there

is insufficient information available at this time to determine whether current uses of triallate pose a mutagenic risk to human populations. As discussed previously, the currently available toxicological data base, when considered in conjunction with the low exposure potential for triallate, indicate that the potential risks of mutagenicity are very low for triallate. Consequently, the Agency has determined that the issuance of an RPAR is not warranted at this time, because several key pieces of data are lacking. The Agency will require additional tests to provide further indication as to whether the chemical presents an unreasonable mutagenic risk to humans.

The following mutagenicity tests are required.[9/] (See also Subsection V.E. below.)

1. For point (gene) mutation: Mammalian cell culture, using the same cell type (mouse lymphoma L5178Y); or CHO, or V79 (i.e., another locus).

2. For chromosome effects: Several tests from the following types:

   a. In vitro cytogenetics, using mammalian cells; or sister chromatid exchange in mammalian cells

3. For DNA damage effects:

   a. In vitro repair assays, either bacterial (e.g., E. coli Pol A; B. subtilis Rec), or mammalian (e.g., unscheduled DNA synthesis)

   b. In vivo cytogenetics, in rats (e.g. micronucleus; or bone marrow.)

   c. Dominant lethal, either in rats, or repeat in mice. This could be combined with sperm morphology, or inhibition of testicular DNA synthesis, or (mouse) spermatocyte test.

9/ Protocols for two tests have been received and approved by the Agency: mammalian cell culture for point mutation; and in vivo cytogenetics in rats.

C. Teratogenic and Fetotoxic Effects

The Agency has determined that the current data base is inadequate to satisfy registration requirements. However, the available study in rabbits by Industrial Bio-Test Laboratories (IBT No. 651-05255 [Calandra, 1974b]) provides a basis on which to conduct a rough, preliminary assessment of the potential teratogenic and fetotoxic effects of exposure to triallate.

The current regulations covering fetotoxic and teratogenic effects require consideration of potential exposure in connection with the issuance of an RPAR. Based on applicator exposure data submitted by Monsanto Company (Arras, 1980) and evaluated by the Agency, total absorbed body doses for applicators working with emulsifiable concentrate triallate during tank fill and application procedures, and during the process of incorporating the herbicide in the soil, have been estimated at roughly 1/500th and 1/1100th, respectively, of the level of exposure at which fetotoxic effects were observed in rabbits (3 mg/kg/day). Total body doses to applicators working with the granular formulation during hopper fill and application procedures, and during the process of incorporating granular triallate into the soil, have been estimated at 1/900th and 1,500th, respectively, of the level at which fetotoxic effects were observed in rabbits. Based on tolerances for triallate, worst-case dietary exposure to the general public has been estimated as roughly 1/19,000th of the level at which fetotoxic effects were observed in rabbits.

Taking into account the decidedly limited toxicological evidence presently available in the IBT test conducted by Calandra (1974b), considered together with the low levels of exposure associated with triallate under current use patterns, the Agency has determined that no rebuttable presumption against triallate on the basis of teratogenic and fetotoxic effects is warranted at this time. Studies on the reproductive, fetotoxic, and teratogenic effects of triallate are required as specified in the Proposed Guidelines for Registering Pesticides in the U.S., 40 CFR 163.83-3 and -4 (Fed. Reg. 43(163):37382-37385 [August 22, 1978]).

D. Neurotoxicity

Regarding acute delayed neurotoxicity as a possible adverse effect of exposure to triallate, the Agency has determined that in view of currently available evidence (IBT Studies, Nos. 8580-09120 and 8580-10814 [Keplinger 1976; 1978]), no trigger has been met and no further testing is necessary.

Regarding the adverse effects reportedly observed in a recent study in which rats were treated with a mixture of chemicals, one of which was triallate, further testing in rats is required to clarify the nature of this potential hazard and to determine a no observable effect level (NOEL). The symptoms observed in rats--including circling behavior, head tremors, and head tilt to one side (symptoms were exacerbated by external stimulation)--were said to have been likewise observed in quail which had been treated with triallate alone, and this suggests that the effects observed in rats might have been due to triallate.

Taking all currently available evidence into account, the Agency has determined that a rebuttable presumption against triallate is not warranted on the basis of neurotoxicity at this time, though the current data base is not sufficient to support registration.

E. Metabolic Effects

A general metabolism study is required to determine absorption, distribution, metabolism, and excretion of triallate in mammals. The study protocol published in the Proposed Guidelines for Registering Pesticides in the U.S., 40 CFR 163.85-1 (Fed. Reg. 43(163):37394-37396 [August 22, 1978]), should be utilized in designing this study. For triallate, the blood kinetics and tissue binding tests will not be required. Since the guidelines are applied on a case by case basis, the registrant should present the protocol to the Agency before starting the study in order to insure that it meets Agency requirements.

VI. BIBLIOGRAPHY

Albert, Roy E., M.D. 1977. The Carcinogen Assessment Group's Preliminary Review of Oncogenicity of Avadex (Diallate and Triallate). With Addendum. (Unpublished.)

Albert, Roy E., M.D. 1979. The Carcinogen Assessment Group's Risk Assessment of Avadex (Diallate and Triallate). Includes Dubin, 1977, as appendix. (Unpublished.)

Andersen, K.J., E.G. Leighty, and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agr. Food Chem. 20: 649-656.

Anderson, Elizabeth L. 1977. Memorandum: Carcinogenic Potential of Triallate (Avadex BW), dated September 21, 1977. From Elizabeth L. Anderson, Executive Director, Carcinogen Assessment Group, to Richard Troast, Project Manager, Office of Special Pesticide Review.

Arras, D.D., R. Lauer, and S. Dubelman. 1980. Applicator Exposure Study for Avadex BW Herbicide under Actual Field Conditions. Monsanto Report MSL-1155. (Confidential.)

Auerbach, Jan. 1979. Memorandum and attachments: Review of IBT Studies on Triallate, dated August 17, 1979. From Jan Auerbach, Chief, Regulatory Analysis and Lab Audits Branch, Special Pesticide Review Division to Bob Brown, Chief, Chemical Review Branch 3, Special Pesticide Review Division.

Bignami, M., F. Aulicino, A. Velich, A. Carere, and G. Morpurgo. 1977. Mutagenic and recombinogenic action of pesticides in Aspergillus nidulans. Mut. Res. 46: 395-402.

Brusick, D.J. 1977a. Mutagenic Evaluation of CP 23426 (Final Report, July 1977). Submitted to Monsanto Co., Inc. by Litton Bionetics, Inc., Project No. 2683. Submitted to EPA March 22, 1978. EPA Accession No. 233353.

Brusick, D.J. 1977b. Mutagenic Evaluation of CP 23426 in the Mouse Lymphoma assay (Final Report, August, 1977). Submitted to Monsanto Co., Inc. by Litton Bionetics, Inc., Project No. 2684. Submitted to EPA March 22, 1978. EPA Accession No. 233353.

Calandra, J.C. (Industrial Bio-Test Laboratories, Inc.). 1974a. Mutagenic Study with Avadex BW in Albino Mice (BTL-74-16). Submitted by Monsanto Company October 1974. (Confidential; unpublished.)

Calandra, J.C. (Industrial Bio-Test Laboratories, Inc.). 1974b. Teratogenic Study with Avadex BW Technical (CP23436) in Albino Rabbits (BTL-74-17). Submitted by Monsanto Chemical Co. January 1975. (Confidential; unpublished.)

Calandra, J.C. (Industrial Bio-Test Laboratories, Inc.). 1976, 1977. Two-Year Chronic Oral Toxicity Study with AVADEX BW Technical in Albino Rats (BTL No. 74-15). With addendum. Individual Animal Data. Submitted by Monsanto Company February 4, 1977. (Confidential; unpublished.)

Carere, A., V.A. Ortali, G. Cardamone, M. Torracea, and R. Reschatti, 1978a. Microbial mutagenicity studies of pesticides in vitro. Mut. Res. 57: 277-286.

Carere, A., V.A. Ortali, G. Cardamone and G. Morpurgo. 1978b. Mutagenicity of dichlorvos and other structurally related pesticides in Salmonella and Streptomyces. Chem. - Biol. Interactions 22: 297-308.

Chernoff. 1977. Memorandum: Review of Teratology Study on Triallate, dated September 23, 1977. From Neil Chernoff, Ph.D., Experimental Biology Division, HERL-RTP (MD-74) to Mr. Richard Troast, WH-566, Project Leader, OSPR [Office of Special Pesticide Reviews].

Cullimore, D. R. and A. E. Smith. 1972. Initial studies on the microbial breakdown of triallate. Bull. Environ. Contam. Toxicol. 7: 36-42.

DeLorenzo, F. N. Staiano, L. Silengo, and R. Cortese. 1978. Mutagenicity of diallate, sulfallate and triallate and relationship between structure and mutagenic effects of carbamates widely used in agriculture. Cancer Res. 38: 13-15.

Dubin, I. N., M.D. 1977. Report on Histopathologic Studies of Monsanto Triallate (Avadex-BW) Experiment on Charles River Albino CD Rats. Included as appendix in Albert, 1979. (Unpublished.)

Edwards, W. Thomas. 1979. Memorandum: Triallate RPAR, dated July 16, 1979. From W. Thomas Edwards, Triallate RPAR Team Member, Pharmacologist, Toxicology Branch, HED (TS-769) to Richard Troast, Project Manager, SPRD (TS-791).

Freudenthal, R. I. and R. P. Leber. 1977. Report on the Evaluation of Diallate/Triallate Toxicity Data to Determine its Potential Health Hazards in Man and Domestic Animals. Battelle Memorial Laboratories, Columbus, Ohio. (Unpublished.)

Grover, R. 1974. Adsorption and desorption of trifluralin, diallate and triallate by various adsorbents. Weed Sci. 22(4): 405-408.

Hance R. J., J. Holroyd, and C. E. McKone. 1973. Some aspects of triallate volatility. Pest. Sci. 4: 13-17.

Innes, J. R. M., B. M. Ulland, M. G. Valerio, L. Petrucelli, L. Fishben, E. R. Hart, A. J. Pollotta, R. R. Bates, H. L. Falk, J. J. Gart, M. Klein, I. Mitchell and J. Peters. 1979. Bioassay of pesticides and industrial chemicals for tumorigencity in mice: a preliminary note. J. Nat. Cancer Inst. 42: 1101.

Jennings, Allen. 1977. Memorandum: Triallate, dated October 4, 1977. From Allen Jennings, Standards and Regulations Evaluation Division, to Richard Troast Project Manager, Office of Special Pesticide Review.

Jensen, Janice. 1980. Data Evaluation--Triallate (Monsanto Report MSL-1155). Completed by Janice Jensen, Environmental Fate Branch.

Keplinger, M.L. (Industrial Bio-Test Laboratories, Inc.). 1976. Neurotoxicity Study with Avadex BW in Chickens. Submitted by Monsanto Company February 16, 1977. (Confidential; unpublished.)

Keplinger, M.L. (Industrial Bio-Test Laboratories, Inc.). 1978. Neurotoxicity Study with Avadex BW in Chickens. Submitted by Monsanto Company July 19, 1978. (Confidential; unpublished.)

Lehman, A. J. 1962. The annual per capital consumption of selected items of food in the United States. Quarterly Bulletin of the Association of Food and Drug Officials 26: 149.

Mauer, Irving. 1980. Memorandum: Mutagenicity of Triallate, dated May 8, 1980. From Irving Mauer, Toxicology Branch, HED, to Minnie Sochard, SPRD, Review Branch 3.

Mitchell, A.D. 1980. An Evaluation of the Mutagenic Potential of Triallate Employing the L5178Y $TK^{+}/^{-}$ Mouse Lymphoma Assay. SRI International, 333 Ravenswood Ave., Menlo Park, CA. 94025.

Mittelman, A. 1978. Memorandum: Triallate Exposure Analysis Review, dated March 16, 1978. From A. Mittelman, Criteria and Evaluation Division, to Richard Troast, Project Manager, Special Pesticide Review Division.

Melnikov, N. W. 1971. In Chemistry of Pesticides, F. A. Canther and J. D. Gunther eds. New York: Springer-Verlag.

Monsanto Co., 1979. Acute Toxicity Studies Submitted in Support of Avadex BW® Herbicide. Monsanto Co. Agricultural Products Co., St. Louis, Mo. EPA Accession No. 241271-6.

Monsanto Co., 1980. Report on triallate. Monsanto Co. Agricultural Products Co., St. Louis, Mo. EPA Accession No. 243009.

Monsanto Co. 1975. Report #524-124 on Triallate. Monsanto Co. Agricultural Products Co., St. Louis, Mo.

Pertel, Ruth. 1977. Memorandum: Triallate mutagenicity, dated August 17, 1977. From Pertel, Ph.D., Project Manager, OSPR, to Richard Troast, Project Manager, OSPR.

Pesticide Petition OP0944. Submitted by Monsanto Chemical Company January 10, 1970. (Confidential.)

Pohlheim, E., F. Pohlheim, and G. Gunther. 1977. Mutagenicity testing of herbicides with a haploid pelargonium. Mut. Res. 46: 232.

Selim, Sami. 1978. Environmental Fate Profile: Triallate. Prepared by Sami Selim, Environmental Fate Branch, Hazard Evaluation Division, Office of Pesticide Programs.

Severn, David J. 1977. Memorandum: Validation of Monsanto Report #524-124 on Triallate, dated February 17, 1977. From David J. Severn, Ph.D., Chemist, Chemistry Branch, C & ED, to Project Manager, OSPR.

Sikka, H. C. and P. Florczyk. 1978. Mutagenic activity of thiocarbamate pesticides in a microbial test system. J. Agr. Food. Chem. 26:146-148.

Simmon, V. F., E. S. Riccio and A. Griffin. 1978. In Vitro Microbiological Mutagenicity Assays of Diallate and Triallate (Final Report, April 1978). Stanford Research Institute International, Project LSU-3493. Prepared for EPA (HERL/RTP) under Contract No. 68-01-2458.

Smith, A. E. 1971. Disappearance of triallate from field soils. Weed Res. 19(5): 536-537.

Smith, A. E. 1970. Degradation, adsorption and volatility of diallate and triallate in prairie soils. Weed Res. 10: 331-339.

Smith, A. E. 1969. Factors affecting the loss of triallate from soils. Weed Res. 9: 306-313.

U.S. Congress, Senate, Committee on Agriculture, Nutrition, and Forestry. 1979. Conference Report on S. 1678. 95th Congress, 2d Session.

Voytenko, G. A., Ye N. Burkatskaya, V. I. Matyuskima, T. V. Dyadicheva, L. A. Matokhnyuk, T. L. Medved, A. G. Pestova, L. G. Aleksandrova, Z. V. Ivanova, and N. G. Stepanchenko. 1972. Inst. Gig. Tr. Profzabol. 16: 4-8.

Appendix: EPA Policy on IBT-Generated Data*

1. The moratorium which has been in effect for all chemicals supported by IBT data is now lifted.

2. In cases where the invalidation of IBT data results in major data gap(s) (see below), the registrant will be required to fill the data gap(s) as soon as possible in accordance with Section 3(c)(2)(B) of FIFRA. Failure to meet the requirements of Section 3(c)(2)(B) will result in suspension of the registration.

3. In cases where the invalidation of IBT data results in minor data gaps, the gaps will be filled through the Registration Standard data call-in process. This will occur over the next one to five years.

4. In cases where virtually the entire data base is invalid and there is a strong possibility of substantial health risk, EPA will consider that the Section 3(c) requirement to provide an adequate basis for the registration of the chemical is unfulfilled by the registrant. In these cases, EPA will consider canceling the current registration of the chemical under Section 6(b) for failure to comply with the requirements of the Act. This cancellation would remain in effect until the studies required under Section 3(c)(2)(B) are completed, reviewed and a determination made on the safety of the chemical. The Agency's determination of strong possibility of substantial health risk will be based on whatever data are available to assess chemical toxicity and consideration of exposure levels of the chemical.

5. In cases where close review of the raw data indicates that some adverse health effects data were not reported to EPA, the registrant will be required to reconduct the studies as soon as possible in accordance with Section 3(c)(2)(B) of the Act. Also, EPA will consider further regulatory action, such as RPAR, expedited RPAR, or conduct of a Section 6(b)(2) hearing. The nature of the regulatory action will depend on the expected level of adverse health risk.

* Issued July 29, 1980

6. Data will be considered invalid for any one of the following reasons:

   a. failure to submit raw data required to be submitted by February 29, 1980,

   b. failure to submit validation of a pivotal study required to be submitted by February 29, 1980, or

   c. determination of invalidation by EPA based on comparison of raw data with the final report originally submitted to the Agency.

7. Determination of whether a data gap is minor or major will be made on a case-by-case basis. In general, however, chronic/oncogenicity studies, three generation reproduction studies, teratology studies and neurotoxicity studies are considered pivotal to the Agency's decision-making process. Therefore, the presence of one or more studies which are invalid due to significant scientific problems in any of these categories would constitute a major data gap. An invalid subchronic study could be considered a major data gap if no longer term study exists in the data base, which addresses the same toxicity endpoint. A minor data gap is, for example, one involving an acute study, or the invalidity of a chronic study due to administrative deficiencies which have little or no influence on the scientific soundness of the study.